(c) purifying the resultant hPTH (1-84) protein.

37. The composition of claim 36, wherein the signal sequence is encoded by the following amino acid sequence:

Met-Asn-Ile-Phe-Tyr-Ile-Phe-Leu-Phe-Leu-Ser-Phe-Val-Gln-Gly-Thr-Arg-Gly.--

REMARKS

Applicants respectfully request formal examination of this application.

I. STATUS OF THE CLAIMS

Claims 1-20 have been cancelled, without disclaimer or prejudice thereof, and claims 21-37 have been added to the application. Applicants reserve the right to prosecute the subject matter of the cancelled claims is this or another application.

New claims 21-23 are directed to a composition comprising human parathyroid hormone (hPTH) (1-84), wherein the hormone has a point mutation at amino acid 26 changing the amino acid from lysine (K26) to glutamine (Q26). The resultant hPTH is superior to wild-type hPHT in that it is resistant to degradation. *See e.g.*, page 17, lines 7-15, of the Application.

Claims 24-29 are directed to a composition comprising hPTH (1-84), wherein the hormone is made using a microorganism comprising the sequence for hPTH and, as a leader sequence, a modified sequence for *Saccharomyces* mating factor α1 (MFα1). For claims 24-26, the MFα1 sequence lacks the yeast STE13 recognition site, and for claims 27-29, the MFα1 sequence comprises only the first 19 amino acids of the sequence.

Claims 30-33 are directed to a composition comprising hPTH (1-84), wherein the hormone is made using a microorganism having a leader sequence and a modified hPTH sequence.

Claims 34-37 are directed to a composition comprising hPTH (1-84), wherein the hormone is made using a microorganism having a leader sequence and either an optimized consensus signal sequence or a functional signal sequence.

Exemplary support provided in the specification for the amended claim and the new claims is given in the following table.

CLAIMS	EXEMPLARY SUPPORT IN SPECIFICATION
21	Page 3, lines 25-27; page 17, lines 11-18; page 22, lines 3-27.
22	Page 20, lines 35-38.
23	Page 20, lines 36-38; page 21, line 36, through page 22, line 2.
24	Page 3, lines 27-30; page 14, lines 20-27; and page 35, line 6, through page 36, line 23.
25, 28	Page 3, lines 10-13; and original claim 10.
26, 29, 33	Page 7, lines 30-32; and page 5, lines 19-22.
27	Page 14, lines 31-35; and page 36, line 25, through page 37, line 35.
30	Page 19, lines 4-17; page 39, lines 7-24; page 37, line 36, through page 38, line 4.
31	Page 14, line 36, through page 15, line 11.
32	Page 6, lines 22-28; page 14, lines 15-20.
34	Page 23, line 30, through page 24, line 29.
35	Page 24, line 30, through page 25, line 36.
36	Page 24, lines 2-7; page 25, lines 3-6.
37	Page 25, line 37, through page 26, line 8.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. SUMMARY OF THE INVENTION

The present invention is directed to a compositions comprising recombinant hPTH. hPTH is an important regulator of calcium metabolism in mammals, and is also related to several mammalian diseases, such as milk fever, acute hypocalsemia, and otherwise pathologically altered blood calcium levels. *See* page 2, lines 15-19, of the Application. Through its action on target cells in bone and kidney tubuli, hPTH increases serum calcium and decreases serum phosphate, while opposite effects are found regarding urinary excretion of calcium and phosphate. *See* page 5, lines 27-31, of the Application. hPTH is useful, for example, as a component of a diagnostic kit or as a therapeutic in human and veterinary medicine. *See* page 2, lines 20-22, of the Application.

Prior to the present invention, hPTH was commercially available only in very small quantities at high cost, partly because synthesis of the compound was difficult and complex.

See page 1, lines 33-38, of the Application. Moreover, recombinant production of hPTH was hampered by the discovery that *E. coli* degrades human hPTH.

Applicants have overcome the problems of the prior art and discovered compositions of recombinant hPTH that can be made in high yield using microorganisms.

The present invention is directed to a composition comprising a modified recombinant hPTH, wherein the modified hPTH is degradation resistant (claims 31, 36, and 37). *See* page 15, lines 18-28, of the Application. The modified hPTH has a correct size, full immunological reactivity with two different specific hPTH antibodies, a correct N-terminal amino acid sequence, and comparable biological activity to the wild-type hPTH. *See* page 15, lines 31-38, of the Application.

In addition, the invention is directed to compositions comprising recombinant hPTH, wherein the hPTH is prepared in microbial cells (claims 24-37). The compositions are made by a process in which (1) the microorganism comprises a modified sequence for *Saccharomyces* MFα1 (claims 24-29); (2) the microorganism comprises a modified hPTH sequence (claims 30-33); and (3) the microorganism comprises either an optimized consensus signal sequence or a functional signal sequence (claims 34-37). *See e.g.,* page 14, lines 20-27 and 31-35; page 19, lines 4-17; page 23, line 30, through page 24, line 29; page 24, lines 2-7; page 24, line 30, through page 25, line 6; and page 35, line 6, through page 37, line 35, of the specification. Such compositions are superior to those known prior to the claimed invention. Compositions according to the claimed invention can be made in dramatically increased yields of, for example, 5- to 10-fold greater than the prior art. *See e.g.,* page 5, lines 6-12; page 14, lines 23-27; and page 17, lines 7-11, of the specification.

III. CONCLUSION

Applicants respectfully request formal examination of the present application in view of the above amendments and remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

Should the Examiner have any questions or comments regarding the pending application or this Amendment, the Examiner is requested to call the undersigned at 202-672-5538.

If there are any fees due in connection with the filing of this Preliminary Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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